

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: Foley & Lardner LLP Washington Harbour, 3000 K Street, NW, Suite 500 Washington 20007, USA		PCT NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty) (PCT Rule 71.1)	
		Date of mailing <i>(day/month/year)</i> - 8 MAR 2006	
Applicant's or agent's file reference 060348/0119		IMPORTANT NOTIFICATION	
International application No. PCT/IB2005/000204	International filing date <i>(day/month/year)</i> 27 January 2005	Priority date <i>(day/month/year)</i> 2 February 2004	
Applicant <p style="text-align: center;">ENGINEIC MOLECULAR DELIVERY PTY LTD. et al</p>			

1.	The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2.	A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3.	Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.
4.	<p>REMINDER</p> <p>The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).</p> <p>Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.</p> <p>For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the <i>PCT Applicant's Guide</i>.</p> <p>The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.</p>

Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929	Authorized officer <p style="text-align: center;">CHRIS LUTON</p> Telephone No. (02) 6283 2256
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PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 060348/0119	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/IB2005/000204	International filing date (<i>day/month/year</i>) 27 January 2005	Priority date (<i>day/month/year</i>) 2 February 2004
International Patent Classification (IPC) or national classification and IPC Int. Cl. A61K 47/00 (2006.01)		
Applicant ENGINEIC MOLECULAR DELIVERY PTY LTD. et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
 - a. ☒ (*sent to the applicant and to the International Bureau*) a total of 3 sheets, as follows:
 - ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
 - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - b. ☐ (*sent to the International Bureau only*) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

<input checked="" type="checkbox"/> Box No. I	Basis of the report
<input type="checkbox"/> Box No. II	Priority
<input checked="" type="checkbox"/> Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/> Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/> Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input type="checkbox"/> Box No. VI	Certain documents cited
<input type="checkbox"/> Box No. VII	Certain defects in the international application
<input checked="" type="checkbox"/> Box No. VIII	Certain observations on the international application

Date of submission of the demand 30 November 2005	Date of completion of this report 01 March 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au	Authorized Officer CHRIS LUTON Telephone No. (02) 6283 2256

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Box No. I Basis of the report

1. With regard to the language, this report is based on:

☒ The international application in the language in which it was filed☐ A translation of the international application into _____, which is the language of a translation furnished for the purposes of:☐ international search (under Rules 12.3(a) and 23.1 (b))☐ publication of the international application (under Rule 12.4(a))☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):☐ the international application as originally filed/furnished☒ the description:

pages 1-55 as originally filed/furnished

pages* received by this Authority on _____ with the letter of

pages* received by this Authority on _____ with the letter of

☒ the claims:

pages as originally filed/furnished

pages* as amended (together with any statement) under Article 19

pages* 56-58 received by this Authority on 18 February 2006 with the letter of 18 February 2006

pages* received by this Authority on _____ with the letter of

☒ the drawings:

pages 1/6-6/6 as originally filed/furnished

pages* received by this Authority on _____ with the letter of

pages* received by this Authority on _____ with the letter of

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.3. ☒ The amendments have resulted in the cancellation of:☐ the description, pages☒ the claims, page 59.☐ the drawings, sheets/figs☐ the sequence listing (*specify*):☐ any table(s) related to the sequence listing (*specify*):4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).☐ the description, pages☐ the claims, Nos.☐ the drawings, sheets/figs☐ the sequence listing (*specify*):☐ any table(s) related to the sequence listing (*specify*):

* If item 4 applies, some or all of those sheets may be marked "superseded."

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: 28

because:

☐ the said international application, or the said claims Nos.

relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos.
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos.
are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claim Nos. 28 (**see extra sheet**)

☐ A meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ Furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ Furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ Pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ A meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims 1-27, 29-30	YES
	Claims	NO
Inventive step (IS)	Claims 1-27, 29-30	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-27, 29-30	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 – WO 2003/033519

D2 – WO 2003/072014

D3 – SUZUKI et al.

NOVELTY (N) Claims 1-27, 29-30

D1 discloses compositions comprising intact minicells containing a therapeutic nucleic acid molecule. A therapeutic nucleic acid molecule is a drug molecule. D1 teaches the purification of minicells to a purity of fewer than one parent cell per 10^9 minicells (page 21, line 8 and examples). As the present invention utilises the same purification methods described in D1, the methods of D1 are presumed to be able to achieve the same purification levels described by the present application. However, the Applicant has restricted claims 1-27 and 29-30 to minicells comprising a small molecule drug and uses thereof. D1 does not disclose the use of minicells for the delivery of small molecule drugs. Therefore claims 1-27 and 29-30 are novel in light of the disclosure of D1.

Neither D2 nor D3 disclose minicells comprising a small molecule drug. Therefore, claims 1-27 and 29-30 are novel in light of D2 and D3.

INVENTIVE STEP (IS) Claims 1-27, 29-30

D1 discloses the use of *intact* minicells to deliver therapeutic nucleic acid molecules. Thus, D1 clearly indicates that intact minicells are capable of delivering their contents into living cells. In light of D1, the skilled addressee would have readily understood that the interior of a minicell could support similar substances to those found in the cytoplasm of bacterial cells, including proteins, nucleic acids and a range of small organic molecules. D3 further demonstrates that therapeutically useful substances may be produced within minicells.

It was submitted that it was unheralded by D1 that drugs could be delivered intracellularly without degradation. However, that is precisely what D1 demonstrates by the delivery of a therapeutic nucleic acid. Thus, D1 actually supports the suggestion that minicells may be used to deliver substances without degradation.

D2 is replete with suggestions that minicells may be used for the delivery of therapeutic substances, including both small molecule drugs and peptide drugs (see paragraphs 34, 666-669 for example). D2 exemplifies the expression of protein substances in minicells (see examples).

(continued on extra sheet ...)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The specification does not adequately demonstrate the purification of minicells to fewer than 1 contaminating cell per 10^9 minicells. Therefore, claims 5 and 6 are not fully supported by the description.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

However, it was submitted that the cited prior art fails to teach how to package a small molecule drug within minicells. It was submitted that the skilled addressee would have looked to the prior art and found reference only to packaging substances in minicells via **expression within the parent cell before budding**. In addition, it was submitted that this is not possible with small molecule drugs and that none of the cited prior art suggests loading minicells from an external source of drug. Consequently, claims 1-27 and 29-30 are considered to involve an inventive step in light of the cited prior art.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box III

Originally-filed claims 8-38 were not searched and therefore not reported on. However, in response to the second International Preliminary Examination Opinion, claims 1-27 and 29-30 have been restricted to minicells comprising a small molecule drug and uses thereof. This restricted subject matter is considered to have been covered by the original search. Consequently, this report has been established in respect of the parts relating to claims 1-27 and 29-30.

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 060348/0119	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/IB2005/000204	International filing date (<i>day/month/year</i>) 27 January 2005	Priority date (<i>day/month/year</i>) 2 February 2004	
International Patent Classification (IPC) or national classification and IPC Int. Cl. <i>A61K 47/00 (2006.01)</i>			
Applicant ENGINEIC MOLECULAR DELIVERY PTY LTD. et al			

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<input checked="" type="checkbox"/> Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
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<input type="checkbox"/> Box No. VII	Certain defects in the international application
<input checked="" type="checkbox"/> Box No. VIII	Certain observations on the international application

Date of submission of the demand 30 November 2005	Date of completion of this report 01 March 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3020	Authorized Officer CHRIS LUTON Telephone No. (02) 6283 2256

Box No. I Basis of the report

1. With regard to the language, this report is based on:

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- ☐ international search (under Rules 12.3(a) and 23.1 (b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

- ☐ the international application as originally filed/furnished
- ☒ the description:
- pages **1-55** as originally filed/furnished
 - pages* received by this Authority on _____ with the letter of _____
 - pages* received by this Authority on _____ with the letter of _____
- ☒ the claims:
- pages _____ as originally filed/furnished
 - pages* _____ as amended (together with any statement) under Article 19
 - pages* **56-58** received by this Authority on **18 February 2006** with the letter of **18 February 2006**
 - pages* received by this Authority on _____ with the letter of _____
- ☒ the drawings:
- pages **1/6-6/6** as originally filed/furnished
 - pages* received by this Authority on _____ with the letter of _____
 - pages* received by this Authority on _____ with the letter of _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☒ the claims, **page 59**.
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: 28

because:

☐ the said international application, or the said claims Nos.

relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos.
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos.
are so inadequately supported by the description that no meaningful opinion could be formed (*specify*)

☒ no international search report has been established for said claim Nos. 28 (*see extra sheet*)

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☐ A meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement		
1. Statement			
	Novelty (N)	Claims 1-27, 29-30	YES
		Claims	NO
	Inventive step (IS)	Claims 1-27, 29-30	YES
		Claims	NO
	Industrial applicability (IA)	Claims 1-27, 29-30	YES
		Claims	NO
2. Citations and explanations (Rule 70.7)	<p>The following documents identified in the International Search Report have been considered for the purposes of this report:</p> <p>D1 – WO 2003/033519 D2 – WO 2003/072014 D3 – SUZUKI et al.</p> <p><u>NOVELTY (N) Claims 1-27, 29-30</u></p> <p>D1 discloses compositions comprising intact minicells containing a therapeutic nucleic acid molecule. A therapeutic nucleic acid molecule is a drug molecule. D1 teaches the purification of minicells to a purity of fewer than one parent cell per 10^9 minicells (page 21, line 8 and examples). As the present invention utilises the same purification methods described in D1, the methods of D1 are presumed to be able to achieve the same purification levels described by the present application. However, the Applicant has restricted claims 1-27 and 29-30 to minicells comprising a small molecule drug and uses thereof. D1 does not disclose the use of minicells for the delivery of small molecule drugs. Therefore claims 1-27 and 29-30 are novel in light of the disclosure of D1.</p> <p>Neither D2 nor D3 disclose minicells comprising a small molecule drug. Therefore, claims 1-27 and 29-30 are novel in light of D2 and D3.</p> <p><u>INVENTIVE STEP (IS) Claims 1-27, 29-30</u></p> <p>D1 discloses the use of <i>intact</i> minicells to deliver therapeutic nucleic acid molecules. Thus, D1 clearly indicates that intact minicells are capable of delivering their contents into living cells. In light of D1, the skilled addressee would have readily understood that the interior of a minicell could support similar substances to those found in the cytoplasm of bacterial cells, including proteins, nucleic acids and a range of small organic molecules. D3 further demonstrates that therapeutically useful substances may be produced within minicells.</p> <p>It was submitted that it was unheralded by D1 that drugs could be delivered intracellularly without degradation. However, that is precisely what D1 demonstrates by the delivery of a therapeutic nucleic acid. Thus, D1 actually supports the suggestion that minicells may be used to deliver substances without degradation.</p> <p>D2 is replete with suggestions that minicells may be used for the delivery of therapeutic substances, including both small molecule drugs and peptide drugs (see paragraphs 34, 666-669 for example). D2 exemplifies the expression of protein substances in minicells (see examples).</p> <p>(continued on extra sheet ...)</p>		

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The specification does not adequately demonstrate the purification of minicells to fewer than 1 contaminating cell per 10^9 minicells. Therefore, claims 5 and 6 are not fully supported by the description.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

However, it was submitted that the cited prior art fails to teach how to package a small molecule drug within minicells. It was submitted that the skilled addressee would have looked to the prior art and found reference only to packaging substances in minicells via **expression within the parent cell before budding**. In addition, it was submitted that this is not possible with small molecule drugs and that none of the cited prior art suggests loading minicells from an external source of drug. Consequently, claims 1-27 and 29-30 are considered to involve an inventive step in light of the cited prior art.

Supplemental Box

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Continuation of: Box III

Originally-filed claims 8-38 were not searched and therefore not reported on. However, in response to the second International Preliminary Examination Opinion, claims 1-27 and 29-30 have been restricted to minicells comprising a small molecule drug and uses thereof. This restricted subject matter is considered to have been covered by the original search. Consequently, this report has been established in respect of the parts relating to claims 1-27 and 29-30.

PCT/IB2005/000204

AP20 Rec'd PCT/PTO 01 AUG 2006
Attorney Docket No. 060348/0119

WHAT IS CLAIMED IS:

1. A composition comprising (i) intact minicells that contain a small molecule drug and (ii) a pharmaceutically acceptable carrier therefor.
2. The composition of claim 1, wherein said composition contains fewer
5 than about 1 contaminating parent bacterial cell per 10^7 minicells.
3. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^8 minicells
4. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^9 minicells
- 10 5. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^{10} minicells
6. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^{11} minicells.
7. A composition consisting essentially of intact minicells that contain a
15 small molecule drug.
8. A targeted drug delivery method that comprises bringing bispecific ligands into contact with (a) bacterially derived minicells that contain a small molecule drug and (b) target mammalian cells, such that (i) said bispecific ligands cause said minicells to bind to said mammalian cells, (ii) said minicells are engulfed
20 by said mammalian cells, and (iii) said small molecule drug is released into the cytoplasm of said mammalian cells.
9. The method of claim 8, wherein said target mammalian cells are non-phagocytic cells.
10. The method of claim 8, wherein said bispecific ligand comprises
25 polypeptide or carbohydrate or glycopeptide.

PCT/IB2005/000204

Attorney Docket No. 060348/0119

11. The method of claim 8, wherein said bispecific ligand comprises a first arm that carries specificity for a bacterially derived minicell surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor.
- 5 12. The method of claim 11, wherein said first arm and said second arm are monospecific.
13. The method of claim 11, wherein said first arm and said second arm are multivalent.
14. The method of claim 11, wherein said minicell surface structure is an
10 O-polysaccharide component of a lipopolysaccharide on said minicell surface.
15. The method of claim 11, wherein said minicell surface structure is a member of the group consisting of outer membrane proteins, pilli, fimbriae, flagella, and cell-surface exposed carbohydrates.
16. The method of claim 11, wherein said mammalian cell surface receptor
15 is capable of activating receptor-mediated endocytosis of said minicell.
17. The method of claim 8, wherein said bispecific ligand comprises an antibody or antibody fragment.
18. The method of claim 8, wherein said bispecific ligand comprises a humanized antibody.
- 20 19. The method of claim 8, wherein said minicell comprises an intact cell wall.
20. The method of claim 8, wherein said small molecule drug is a chemotherapeutic agent.
21. The method of claim 8, wherein said mammalian cells are *in vitro*.
- 25 22. The method of claim 8, wherein said mammalian cells are *in vivo*.

PCT/IB2005/000204

Attorney Docket No. 060348/0119

23. A drug delivery method that comprises bringing bacterially derived minicells that contain a small molecule drug into contact with mammalian cells that are phagocytosis- or endocytosis-competent, such that said minicells are engulfed by said mammalian cells and said small molecule drug is released into the cytoplasm of
5 said mammalian cells.

24. The method of claim 23, wherein said minicells comprise an intact cell wall.

25. The method of claim 23, wherein said small molecule drug is a chemotherapeutic agent.

10 26. The method of claim 23, wherein said minicells are *in vitro*.

27. The method of claim 23, wherein said minicells are *in vivo*.

28. A method of loading minicells with a drug, comprising the step of creating a concentration gradient of said drug between an extracellular medium containing said minicells and the minicell cytoplasm, such that said drug moves down
15 said concentration gradient, into the minicell cytoplasm.

29. A composition comprising (i) a bacterially derived minicell that contains a small molecule drug molecule and (ii) a bispecific ligand that is capable of binding to a surface component of said minicell and to a surface component of a non-phagocytic mammalian cell.

20 30. Use of bacterially derived intact minicells and bispecific ligands in the preparation of a medicament, said minicells containing a small molecule drug and said bispecific ligands being capable of binding to said minicells and to target non-phagocytic mammalian cells, for use in a method of treating a disease or modifying a trait by administration of said medicament to a cell, tissue, or organ.